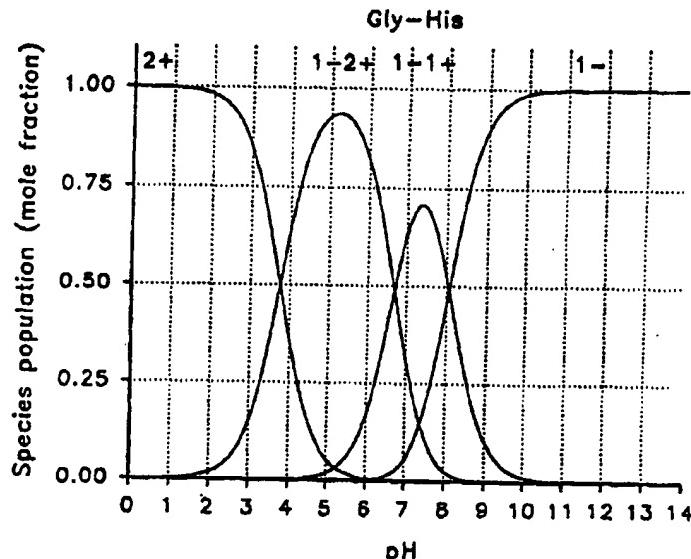




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(54) Title: **BUFFERED DRUG FORMULATIONS FOR TRANSDERMAL ELECTROTRANSPORT DELIVERY**

## (57) Abstract

Buffered drug formulations for transdermal electrotransport delivery are disclosed. The formulations utilize a dipeptide as a buffer and allow for more efficient electrotransport delivery of drugs, e.g., polypeptide drugs, via the transdermal route.

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1      Claims:

2                1. A formulation for transdermal electrotransport delivery,  
3   comprising an aqueous solution of a drug or an electrolyte and a dipeptide  
4   buffer, the dipeptide buffer comprising a polypeptide chain of 2 to 5 amino  
5   acids and having an isoelectric pH at which the dipeptide carries no net  
6   charge, the dipeptide having at least 2 pKa's which are separated by no more  
7   than about 3.5 pH units, the solution having a pH which is within about 1.0 pH  
8   unit of the isoelectric pH.

9

10                2. The formulation of claim 1, wherein the isoelectric pH of the  
11   dipeptide is between about 3 and 10.

12

13                3. The formulation of claim 1, wherein the dipeptide is present  
14   in the solution at a concentration of at least about 10 mM.

15

16                4. The formulation of claim 1, wherein the dipeptide includes at  
17   least one amino acid selected from the group consisting of His, Tyr, Arg, Cys,  
18   Lys, Asp and Glu.

19

20                5. The formulation of claim 1, wherein the dipeptide includes  
21   His.

22

23                6. The formulation of claim 1, wherein the dipeptide is Gly-His.

24

25                7. The formulation of claim 1, wherein dipeptide is selected  
26   from the group consisting of Asp-Asp, Gly-Asp, Asp-His, Glu-His, His-Glu,  
27   His-Asp, Glu-Arg, Glu-Lys, Arg-Glu, Lys-Glu, Arg-Asp, Lys-Asp, His-Gly, His-  
28   Ala, His-Asn, His-Citruline, His-Gln, His-Hydroxyproline, His-Isoleucine, His-  
29   Leu, His-Met, His-Phe, His-Pro, His-Ser, His-Thr, His-Trp, His-Tyr, His-Val,  
30   Asn-His, Thr-His, Try-His, Gin-His, Phe-His, Ser-His, Citruline-His, Trp-His,  
31   Met-His, Val-His, His-His, Isoleucine-His, Hydroxyproline-His, Leu-His, Ala-

1 His, Gly-His, Beta-Alanylhistidine, Pro-His, Carnosine, Anserine, Tyr-Arg,  
2 Hydroxylysine-His, His-Hydroxylysine, Ornithine-His, His-Lys, His-Ornithine  
3 and Lys-His.

4

5               8. The formulation of claim 1, wherein the drug comprises a  
6 polypeptide or a protein.

7

8               9. A transdermal electrotransport drug delivery device (10)  
9 having a reservoir (26, 28) containing the formulation of claim 1.

10

11               10. A transdermal electrotransport drug delivery device (10)  
12 having a drug-containing donor reservoir (26, 28) containing the formulation  
13 of claim 1.

14

15               11. A transdermal electrotransport drug delivery device (10)  
16 having a electrolyte-containing counter reservoir (26, 28) containing the  
17 formulation of claim 1.

18

19               12. A method of buffering an aqueous solution of a drug or an  
20 electrolyte used for transdermal electrotransport delivery, comprising buffering  
21 the solution with a dipeptide comprising a chain of 2 to 5 amino acids and  
22 having an isoelectric pH at which the dipeptide carries no net charge, the  
23 dipeptide having at least 2 pKa's which are separated by no more than about  
24 3.5 pH units, the solution having a pH which is within about 1.0 pH unit of the  
25 isoelectric pH.

26

27               13. The method of claim 12, wherein the isoelectric pH of the  
28 dipeptide is between about 3 and 10.

29

30               14. The method of claim 12, wherein the dipeptide is present in  
31 the solution at a concentration of at least about 10 mM.

1           15. The method of claim 12, wherein the dipeptide contains one  
2       or more of His, Tyr, Arg, Cys, Lys, Asp and Glu.

3

4           16. The method of claim 12, wherein the dipeptide contains His.

5

6           17. The method of claim 12, wherein the dipeptide is Gly-His.

7

8           18. The method of claim 12, wherein dipeptide is selected from  
9       the group consisting of Asp-Asp, Gly-Asp, Asp-His, Glu-His, His-Glu, His-Asp,  
10      Glu-Arg, Glu-Lys, Arg-Glu, Lys-Glu, Arg-Asp, Lys-Asp, His-Gly, His-Ala, His-  
11      Asn, His-Citruline, His-Gln, His-Hydroxyproline, His-Isoleucine, His-Leu, His-  
12      Met, His-Phe, His-Pro, His-Ser, His-Thr, His-Trp, His-Tyr, His-Val, Asn-His,  
13      Thr-His, Try-His, Gin-His, Phe-His, Ser-His, Citruline-His, Trp-His, Met-His,  
14      Val-His, His-His, Isoleucine-His, Hydroxyproline-His, Leu-His, Ala-His, Gly-  
15      His, Beta-Alanylhistidine, Pro-His, Carnosine, Anserine, Tyr-Arg,  
16      Hydroxylysine-His, His-Hydroxylysine, Ornithine-His, His-Lys, His-Ornithine  
17      and Lys-His.

18

19           19. The method of claim 12, wherein the drug comprises a  
20       polypeptide or a protein.

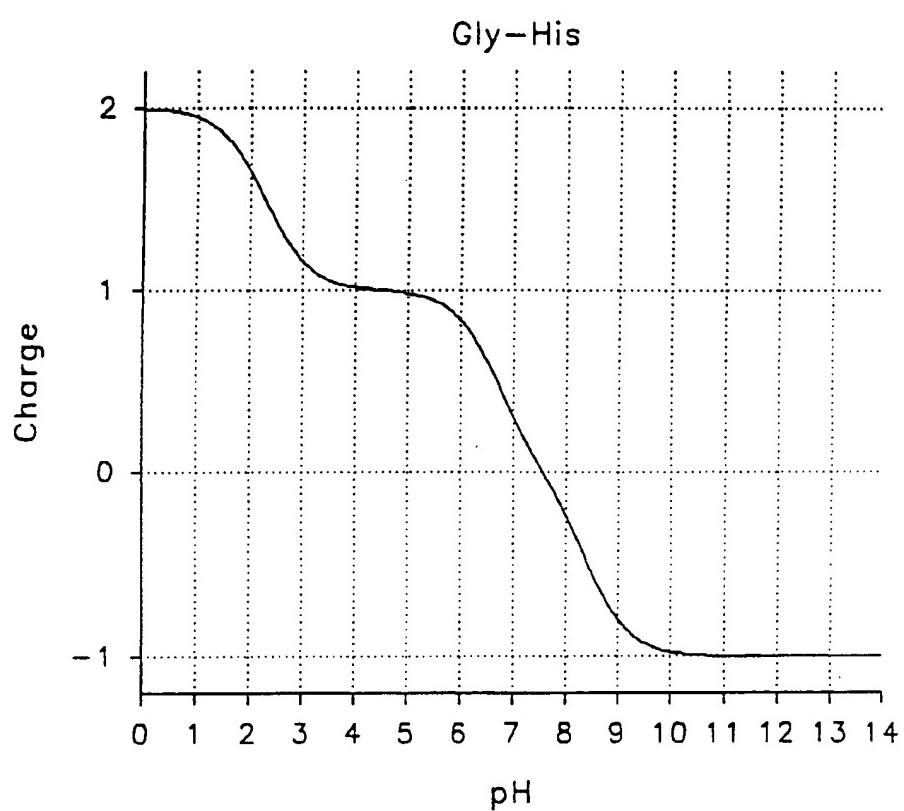
21

22           20. The method of claim 12, wherein the solution is contained  
23       in a reservoir of a transdermal electrotransport drug delivery device.

24

25

26



**FIG. 1**

2/11

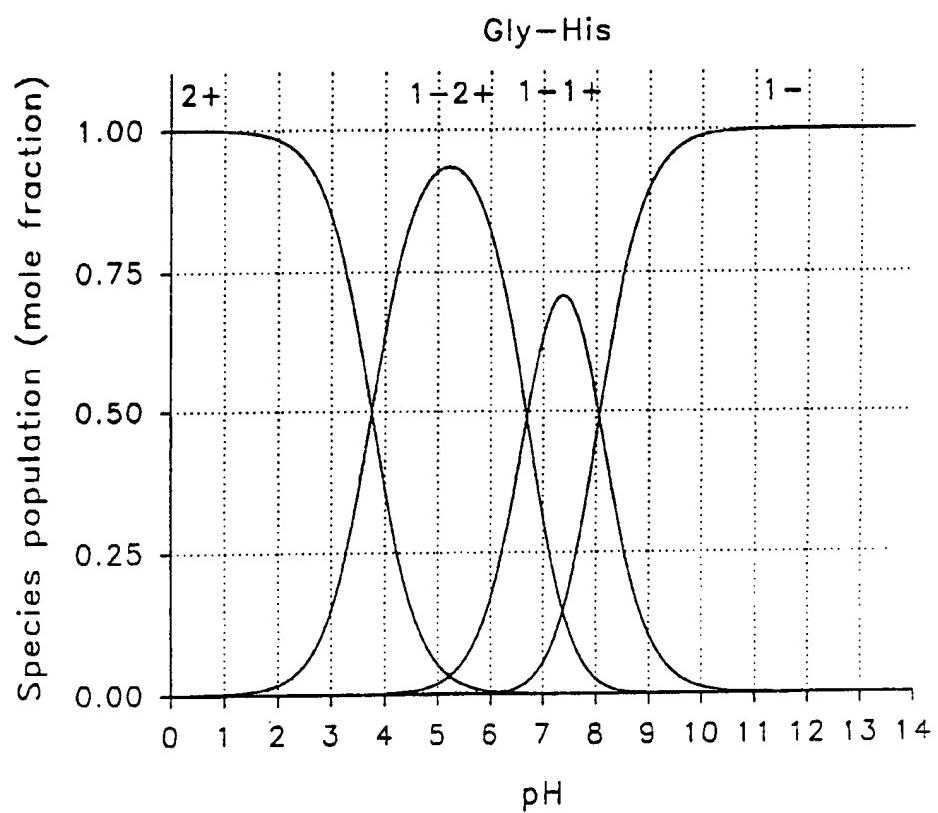


FIG. 2

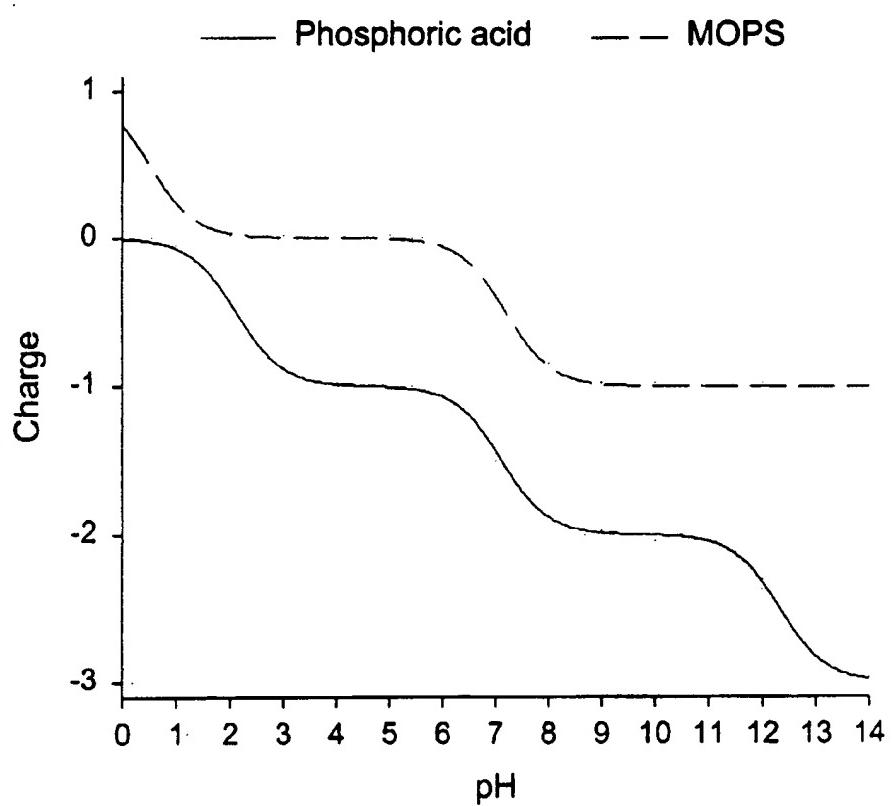
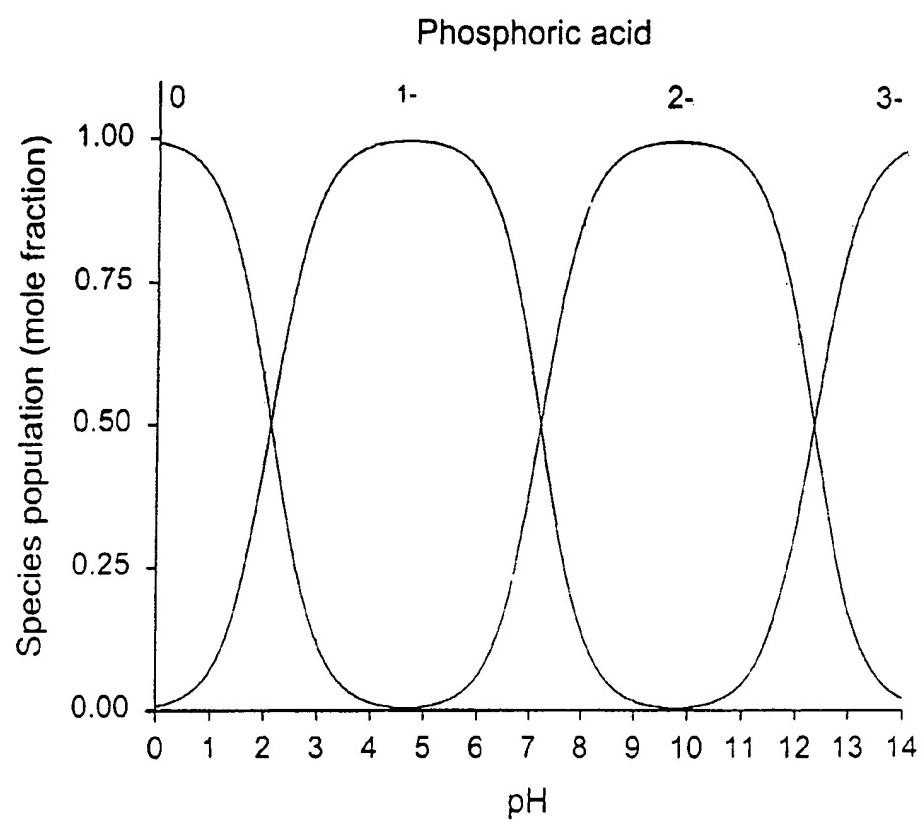
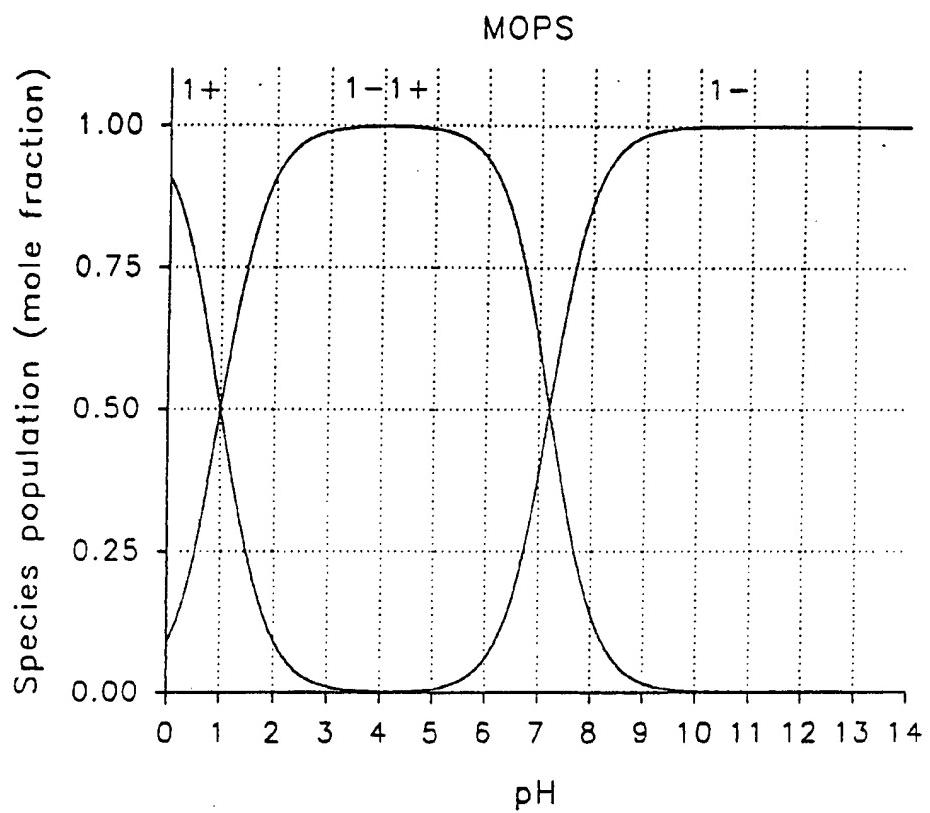
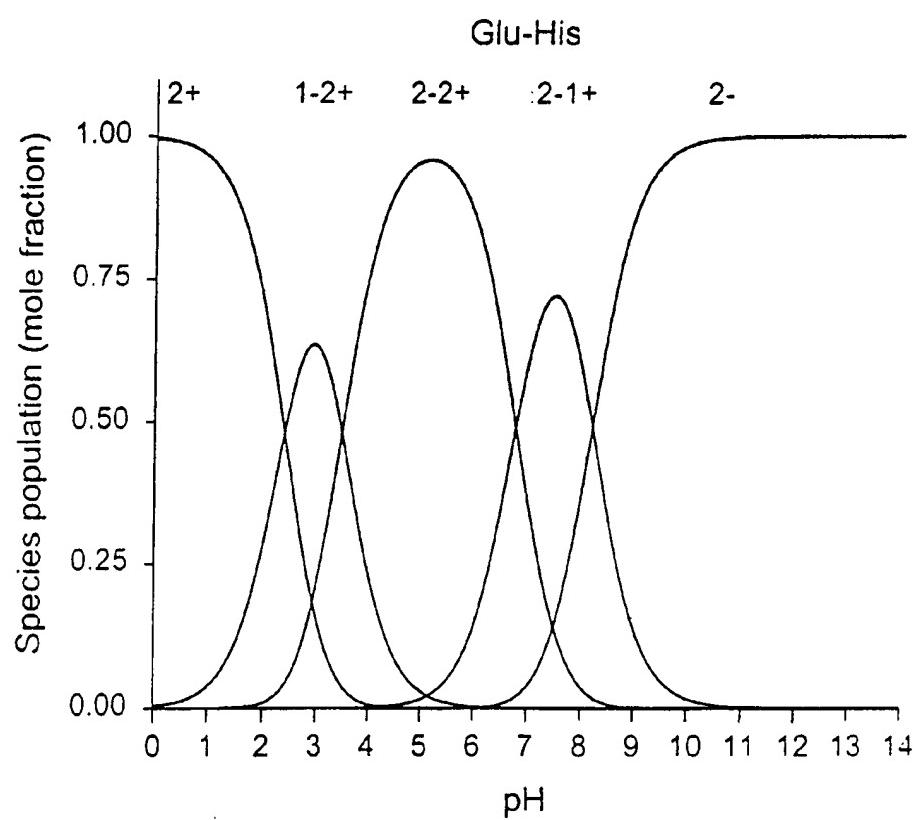


FIG. 3



**FIG. 4**

**FIG. 5**



**FIG. 6**

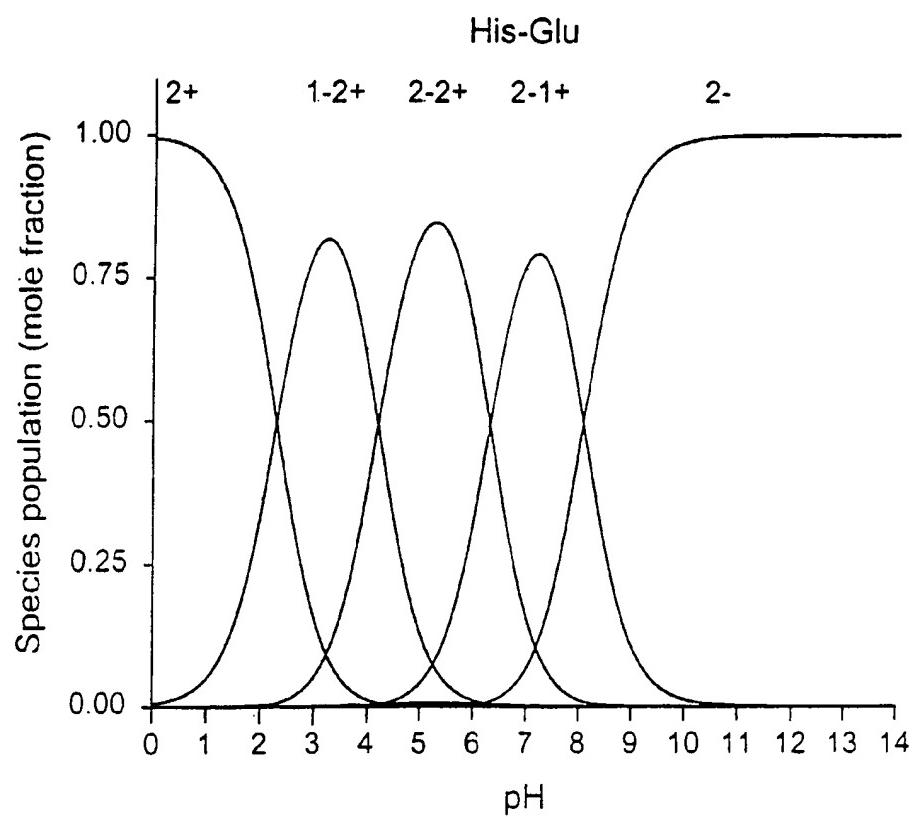
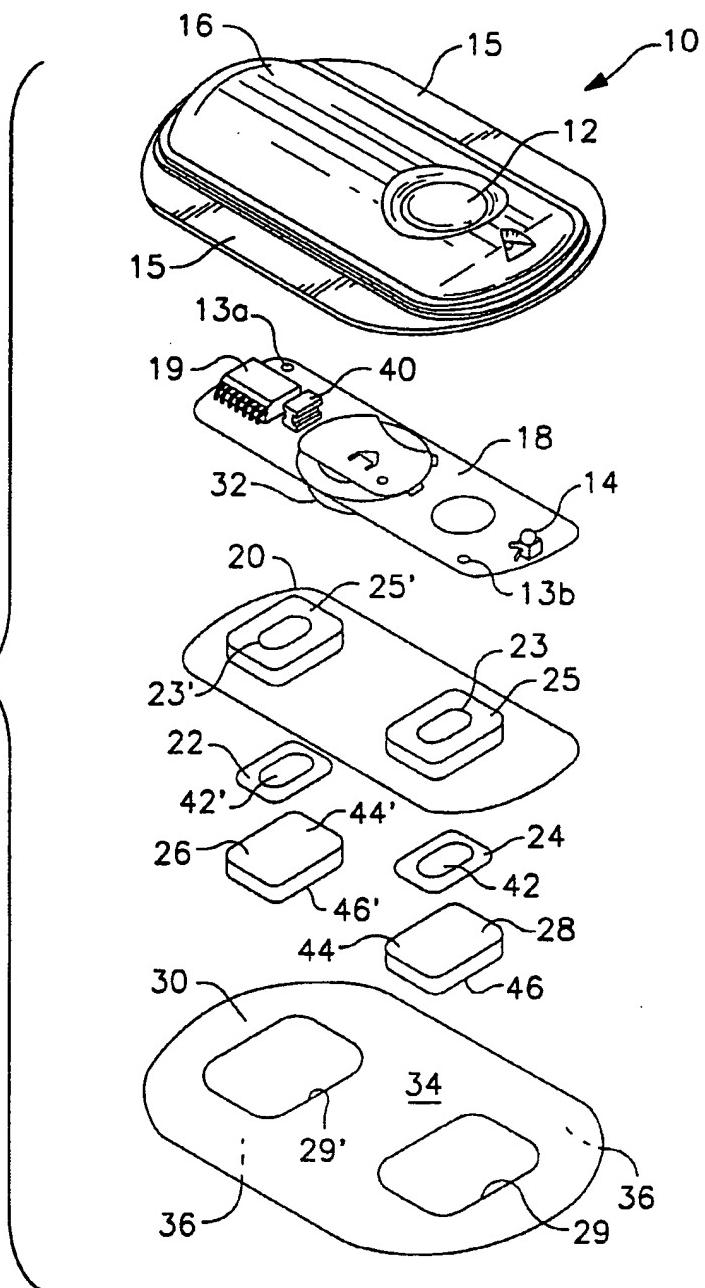


FIG. 7

FIG. 8



9/11

SEC  
RP  
IE

FIG. 9

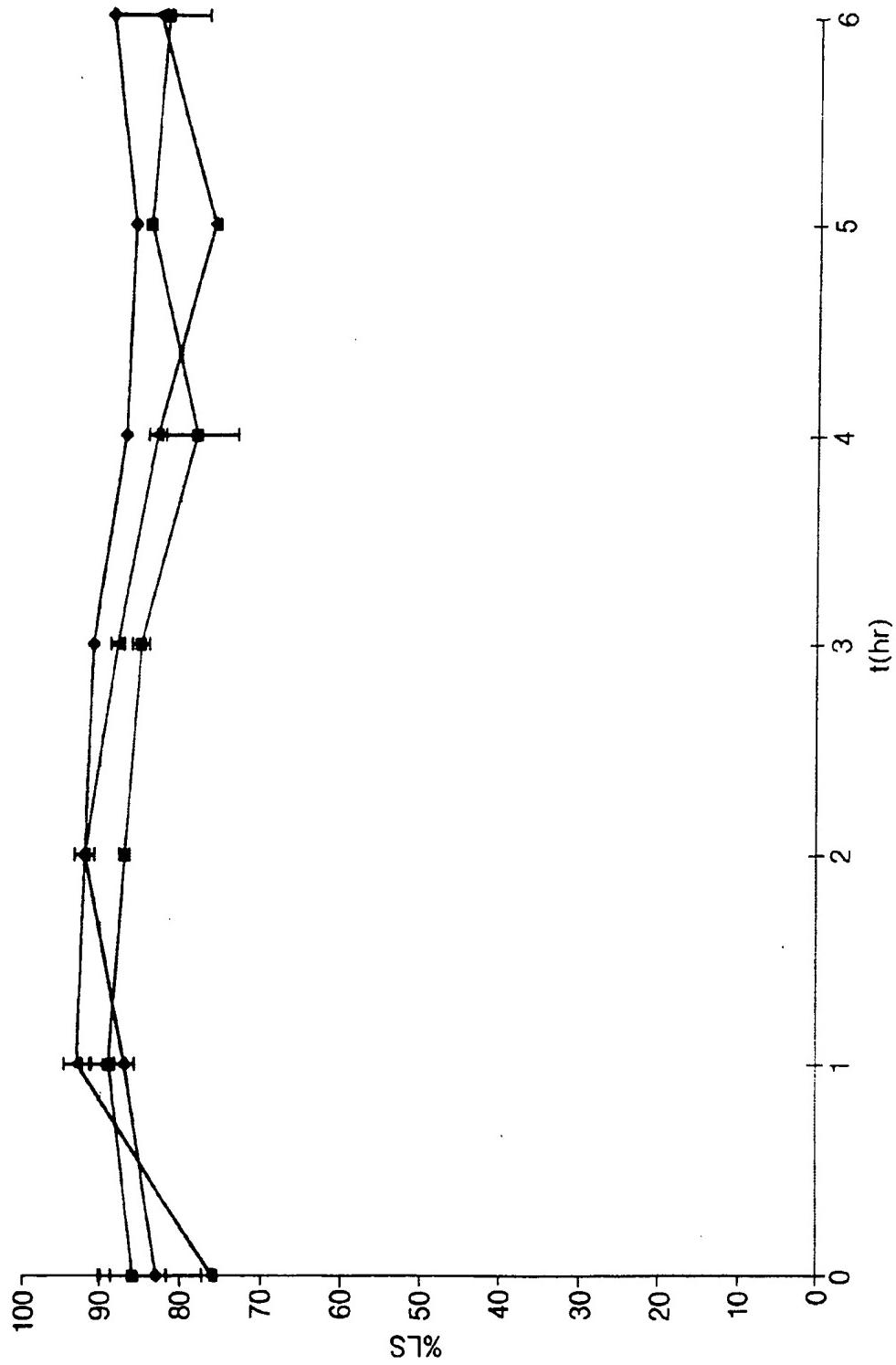
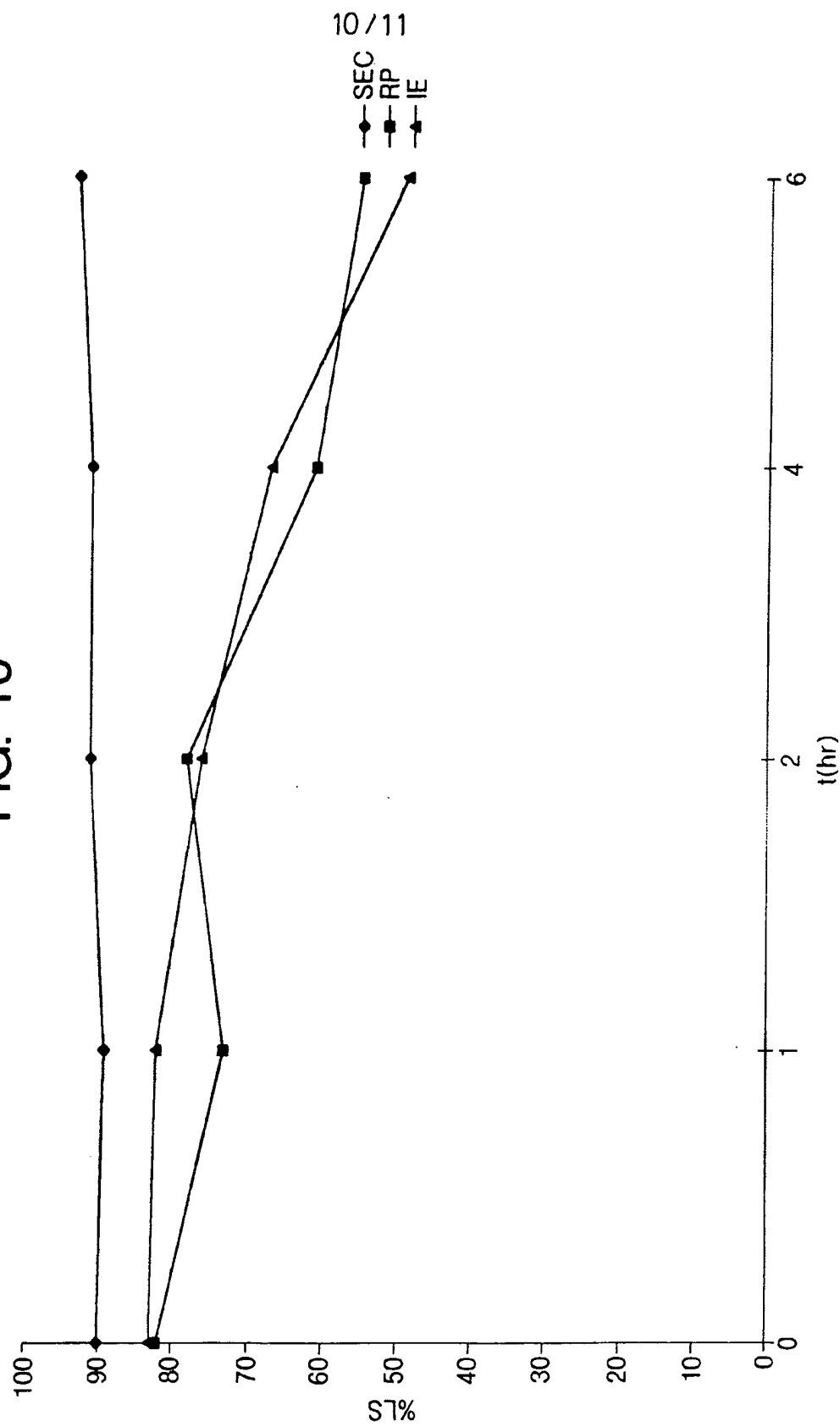
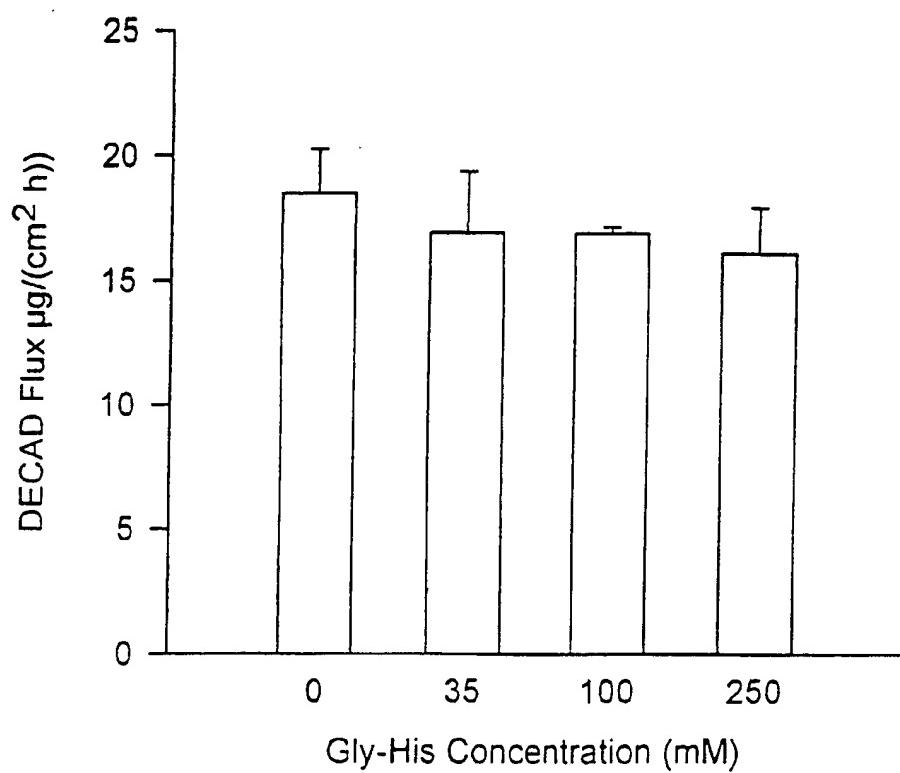


FIG. 10



11/11

**FIG. 11**